REMARKS

Applicants have amended claims 1, 47, and 48 in order to expedite prosecution in this matter. Applicants have amended claim 7 to include prostate cancer. Please cancel claims 43-46 and add new claim 81.

Amendments to the claims are supported throughout the specification and in the claims as originally filed. In particular, recitation of "...contacting the urine sample with an antibody specifically reactive with NGAL ..." as amended Claim 1 is supported at page 18, lines 12-14; at page 25, lines 8-9; and at page 27, lines 9-16. Claims 47 and 48 have been amended for proper dependency. Support for amended claim 7 is found at page 3, lines 16-17, and in claims 4 and 5 as originally filed. New claim 81 is supported in the specification at page 18, lines 12-14 and at page 21, lines 21-23. As such, these amendments to not constitute new matter and their entry is respectfully requested.

With respect to the objection to the specification, the Applicants have deleted the reference to the publication in question that is cited on page 1.

Claims 1, 2, 6, 7, 10, 41-48 were rejected under 35 U.S.C §102(b) as being anticipated by Moses et al (cancer Research, 1998, Vol. 58, pp. 1395-1399) as evidenced by Yan et al (Journal of Biological Chemistry, 2001, vol. 276, Vol. 40, pp 37258-37266).

Applicants respectfully submit that, in light of the claim amendments, this rejection should be withdrawn. Until the present invention, it was not known that the 125 kDa species of Moses et al. was, in fact, MMP-9/NGAL. There is no teaching in Moses et al. that the 125 kDa species is a complex. Further, there is no teaching or suggestion that the 125 kDa species comprises MMP9 or NGAL.

Applicants respectfully submit that one would not be motivated to look for a 125 kDa complex using an antibody specifically reactive with NGAL, as it was unknown that the NGAL was part of the 125 kDa species. Accordingly, one skilled in the art would not know by reading Moses et al. that a tissue remodeling-associated condition, such as breast cancer, could be

diagnosed by detecting an MMP9/NGAL complex using an antibody specifically reactive with NGAL.

Claims 1, 2, 6, 7, 9, 46 and 48 were rejected were rejected under 35 U.S.C §102(b) as being anticipated by Zucker (WO 93/20447) as evidenced by Kolkenbrock et al (Biological Chemistry, 1996, vol. 377, pp. 529-533).

The Applicants respectfully submit that the rejection should be withdrawn because the combination of references does not teach or suggest the invention.

The Examiner states that Zucker discloses a non-invasive method of diagnosing metastatic gastrointestinal cancer comprising analyzing **plasma** for the presence of MMP-9 and TIMP-1/MMP-9 complexes by an Elisa Immunoassy (page 18). The Examiner further contends that Kolenbrock et al. discloses that TIMP-1 was exclusively bound to the monomer/lipocalin complex (page 532, lines 12-17), providing evidence that the MMP-9-TIMP-1 complex detected in the method of Zucker further comprised lipocalin.

The Applicants respectfully disagree with the contention that the MMP-9-TIMP-1 complex detected in the method of Zucker also comprised lipocalin as evidenced by Kolkenbrock et al.. Kolkenbrock et al. does not teach that the binding of TIMP-1 requires the complex of MMP-9 and NGAL, rather than MMP-9 alone. Kolkenbrock et al. isolated three forms of MMP-9 by chromatography on gelatin-Sepharose and heparin-ultragel. The fact that Kolkenbrock et al. did not isolate a TIMP-1/MMP-9 complex in the absence of NGAL could be due to the method of isolation. Isolation of complexes by chromatography is affected by the conditions of the buffer used in the chromatographic separation (e.g. salt concentrations). Kolkenbrock et al. even state that their inability to detect TIMP-1 with monomer or homodimer could be due to a higher affinity of the monomer/lipocalin complex to TIMP-1.

> "We could not find measurable complex formation between TIMP-1 and monomer or homodimer. **It remains to be clarified** if this is due to a higher affinity of the monomer/lipocalin complex to TIMP-1." (See page 532, column 1, lines 13-17)

Thus, their inability to detect MMP-9 complexed to TIMP in the absence of NGAL does not mean that TIMP requires the complex of MMP-9 and NGAL to bind. TIMP-1 may simply bind to MMP in the absence of NGAL with a lower affinity and the complex is undetectable by their

separation method. In fact, MMP-9 is known to bind TIMP-1 in the absence of NGAL. See the studies of Olson et al. **(Exhibit 1)** that determine the kinetics of MMP-9 binding to TIMP-1 in the absence of NGAL (Figure 2A and 2B) and show that pro-MMP-9 and active MMP-9 binds to TIMP-1 (page 29977, column 2, para. 3, lines 9-12).

If the prior art reference does not expressly set forth a particular element of the claim, that reference still may anticipate if that element is "inherent" in its disclosure. However, to establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 20 U.S.P.Q.2d 1746, 1749 (Fed.Cir. 1991). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id. at* 1269, 948 F.2d 1264, 20 U.S.P.Q.2d at 1749 (quoting, *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981)).

Applicants submit that the detection of MMP-9/TIMP-1 complex in Zucker does not inevitably mean detection of MMP-9/NGAL. As such, the Applicants respectfully submit that the rejection should be withdrawn.

Claims 1, 2, 6, 7, 9, 46-48 were rejected under 35 U.S.C. §103(a) as being unpatenable over Zucker (WO 93/20447) as evidenced by Kolkenbrock et al (Biological Chemistry, 1996, vol. 377, pp. 529-533) in view of Kerr and Thorpe (Immunochemistry LabFax, 1994, pp. 1152).

Applicants respectfully submit that this rejection should be withdrawn based on the arguments stated above, and incorporated herein, for the rejection of claims 1, 2, 6, 7, 9, 46 and 48 under 35 U.S.C §102(b) as being anticipated by Zucker (WO 93/20447) as evidenced by Kolkenbrock et al (Biological Chemistry, 1996, vol. 377, pp. 529-533).

In addition, Zucker et al. only exemplify the detection of matrix metalloproteinase inhibitor complexes in a biological sample of **plasma**. Zucker et al. does not exemplify detection of MMP in **urine**. The possibility that a biological sample can be urine is only mentioned in a "laundry list" of biological samples. One skilled in the art would not necessarily expect every protein found in plasma to be present in urine. Thus, Zucker et al. teaching of the MMP-9/TIMP-1 complex in plasma would not direct the skilled artisan to look for MMP-

9/NGAL in urine. Kolkenbrock et al. and Kerr & Thorpe do not make up for this deficiency. As the present invention is directed to detection of a MMP-9/NGAL complex in **urine**, Zucker as evidenced by Kolkenbrock et al. in view of Kerr and Thorpe does not render the present invention obvious.

Accordingly, the Applicants respectfully request that the rejection be withdrawn.

Claims 1, 2, 6, 7, 9, 43-46 were rejected under 35 U.S.C. §103(a) as being unpatenable over Zucker (WO 93/20447) as evidenced by Kolkenbrock et al (Biological Chemistry, 1996, vol. 377, pp. 529-533) and Moses et al. (cancer Research, 1998, Vol. 58, pp. 1395-1399).

Applicants respectfully submit that the amendments to the claim have obviated the rejection, which should therefore be withdrawn. As noted above, the claim now is related to the use of antibodies directed against NGAL. This is not taught or suggested by the cited references.

In view of the following, Applicants respectfully submit that all claims are in condition for allowance. Even if the Examiner disagrees, Applicants respectfully submit that the amendments to the claims, which merely incorporate recitations of claims already being examined, reduces the issues for appeal and thus this amendment should be entered. Early and favorable action is requested.

Respectfully submitted,

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